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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,386	11/13/2006	Toshisada Yano	07541.0009	9341

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EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
01/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,386	YANO ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment and response filed by applicants dated Nov. 11, 2009 have been entered and considered carefully.

Claims 1-18 are pending.

2. The rejection of claims 1-9 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the scope of "solvates" is dropped in view of the limitation in the amendment to *hydrates*.

3. Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the compounds in treating *stroke, head injury, Alzheimer's disease, Parkinson's disease or tinnitus*. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

On pages 8-10 of the response, applicants' recited the description of NR2B receptor activities and the compounds being antagonistic of the NR2B receptor and argued that "*...the written description requirement may be satisfied even without working or prophetic examples...*". While the written description can be satisfied without working example, in this application, the specification explicitly *disclosed* that antagonist of NR2B such as the claimed compounds, have deteriorating effect on learning or memory. It was clearly delineated in the previous office action that the specification disclosed:

> *Abstract*
> *Aingly have completed the following inventions.*
> *piperidine derivative of the formula (I) is found to bind specifically with the NR1/**NR2B** receptor and usable as an analgesic (pain treatment drug).*
> *[0005] ..... Recently, cloning of genes of the NMDA receptor has been done from brains of rats and mice to make it clear that the NMDA receptor is composed of two subunits of NR1 and **NR2** (reference to Non-patent Documents Nos. 3 and 4). The **NR2** subunit contains four subfamilies (**NR2A**, 2B, 2C, and 2D) (reference to Non-patent Document Nos. 5 and 6). It is said that the NR1/**NR2A** receptors are mainly relevant to*

*development of memory and learning acquirement and that the NR1/**NR2B** receptor is mainly relevant to nerve degeneration cell death and transmittance of pains (reference to Non-patent Document Nos. 7 and 8).*
*[0007] However, since the competitive NMDA receptor antagonists may possibly antagonize not only the NR1/**NR2B** receptor but also NR1/**NR2A** receptor, in the case of long time administration of the drugs for Alzheimer's disease or the like, there is a risk of deterioration of learning capability and memory formation.*
*[0031] Based on the results of investigations, inventors of the present invention have found that certain kinds of piperidine derivatives cause strong antagonistic actions for the NR1/**NR2B** receptor and a remarkable analgesic effect and causes no side effect such as psychotic disturbance and accordingly have completed the following inventions.*

The above description clearly identified that NR2A and NR2B are *different* subsets of NMDA receptor and long time administration of nonspecific NR2B antagonists will cause *deterioration of learning and memory*. While the specification provided using of compounds and dosage for treating pain based on NR2B antagonistic activity of the claimed compounds, there is no description as to the physiological activity of the NR2A receptor, how it interacts with the NR2B receptor or reducing to practice of the compounds being able to have efficacy on the NR2A receptor independent of NR2B binding. Attorney's argument, that description with respect to NR2B is sufficient for both receptor activities, is contrary to the disclosure that NR2B and NR2A are different receptors and nonspecific binding of NR2B exerted on NR2A is the deteriorating effect.

There is no description as to the claimed compounds, which antagonistically bind NR2B receptor, which results in *deteriorating* effect on learning and memory, i.e. the compounds will cause learning and memory "loss", thus, how to conduct a process of "treating" or "relieving" learning and memory deficit be accomplished using such a compound.

Further, in absence of nexus, there is insufficient provision in the specification how to manufacture a "medicament" for treating stroke, head injury, Parkinson's disease or tinnitus with effective dosage. There is no actual reduction to practice of such a composition or process for treating the above condition. The pharmaceutical compound art is highly unpredictable especially in the field of NMDA receptor art, it is well recognized that many receptor subunits have been identified which are different in properties, physiological functionality and binding requirement. The specification with limited description of formula I being NR2B receptor antagonists is in sufficient in providing "written description" for the broad scope of making

composition and treating stroke, head injury, Parkinson's disease or tinnitus. Especially, nonspecific binding of NR2B receptor will cause learning deteriorating or memory loss.

4. The rejection of claims 1-9 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement of "solvates" is dropped in view of the limitation in the amendment to *hydrates*.

5. The rejection of claims 1-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reason of record.

Attorney argued that there is "..a strong presumption that a specification having a disclosure which contains a teaching of the manner and process of making and using an invention complies with the enablement requirement unless there is a reason to doubt the objective truth of the statement in the specification..." and alleged that the Office fails to offer sufficient reason or evidence why one or ordinary skill in the art would not be able to practice the claims.

In the previous office action, it was clearly identified that the *specification* described that NR2A and NR2B are *different* subsets of NMDA receptor and long time administration of nonspecific NR2B antagonists will cause deterioration of learning and memory. Therefore, contrary to attorney's argument, the specification taught that an effective NR2B antagonist will "cause" instead of treating learning and memory. There is no enablement as to at what dose, at what site of administration, in what formulation that such a paining killing "deterorating agent" can be made useful in treating stroke, head injury, Alzheimer's disease, Parkinson's disease or tinnitus. There is no delineation how NR2B and NR2A receptor interact and absent of factual support, no nexus was provided that the process of making "analgesic" composition and treating pain would have any efficacy in treating non-pain related disorders such as stroke, head injury, Alzheimer's disease, Parkinson's disease or tinnitus. Especially, the pain relieve dosage was known to have *deteriorative* effect on symptoms of these other disorders. Therefore, clear and sufficient reason have been provided.

6. Claims 1-18 being drawn to compounds of formula I and pharmaceutically acceptable acid addition salts being useful in manufacturing analgesic compositions or used as analgesic i.e. treating pain are allowable. Structurally closest compound is found in Amsterdam et al. WO 02/30422 see p.12 second from bottom. The difference is that the prior art compound does not have R2 being hydroxyl. Modification of the prior art compound to the instant claims is lacking since the compound is sigma receptor binding. Other analogous art such as US 7,435,744; Collins et al. CA 100:79478; Casanova et al. FR 2105119 or Pinard et al. disclosed structural close analgesic compound wherein the linker between the phenyl ring and the piperidinyl ring does not contain a "oxo" substitution. Oxo substituted linker were contemplated but with less desirable activity (see Pinard p.2175 table 1, compound 17). Therefore, no suggestion to modify attributes of the prior art compounds with particularity of the instant claims.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 11, 2010

/Celia Chang/
Primary Examiner
Art Unit 1625